

THE VALUE OF ROUTINE HISTOLOGICAL EXAMINATION OF CURETTINGS
IN ALL FIRST AND SECOND TRIMESTER ABORTIONS

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M.MED. PART III DISSERTATION (OBSTETRICS & GYNAECOLOGY)

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in fulfilment of the requirements for the degree of
Master of Medicine (Obstetrics & Gynaecology)
Part III

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1. ABSTRACT

A prospective study was carried out to assess whether, in first and second trimester abortions, the clinical diagnosis together with the macroscopic appearance of the curettings was an accurate guide to the correct diagnosis, and whether routine histological examination of all curettings was therefore necessary.

The study included 1 464 consecutive patients presenting to the Gynaecology Department at Groote Schuur Hospital, Cape Town with clinically diagnosed abortions during the period 1st February 1988 to 31st December 1988. The correlation between the macroscopic appearance and histological examination compatible with the diagnosis of abortion was found to be 86%. Where the diagnosis was in doubt this correlation was lower. The sensitivity of using the macroscopic appearance as a screening test for the diagnosis of abortion was 96%, with a positive predictive value of 91%. The kappa statistic of agreement between macroscopic appearance and histology was 0,26. The incidence of gestational trophoblastic disease in this series was 0.06%. The diagnosis of ectopic pregnancy was not aided by the use of routine histology.

2. INTRODUCTION

An abortion, the expulsion of a fetus or products of conception of less than 500g, is traditionally managed by evacuation of the uterus. The curettings obtained are usually submitted for histological examination. The rationale behind this is, firstly, to confirm that an intrauterine pregnancy has existed and, secondly, to exclude other conditions which may present in a similar manner, as well as to exclude gestational trophoblastic disease which is potentially premalignant.

Many gynaecological authorities (Novak 1962, Jeffcoate 1975) state emphatically that histological examination of all curettings is obligatory. While this approach has been accepted without question in many gynaecological units throughout the world, its actual effectiveness in achieving the above aims has not been evaluated. In addition, the cost in terms of labour and expertise with regard to the gynaecological staff, nursing staff, laboratory staff and pathology staff has not been considered.

This study was designed to investigate the value of routinely sending curettings from abortions for histological examination, and to assess the correlation between the macroscopic appearance of the curettings and the subsequent histology.

A study of this nature of necessity encompasses a broad understanding of the various factors involved in abortions and this necessitates a study of these factors in some detail.

The conceptus consists of 3 components; decidua, placenta and embryo/fetus. Products of conception

submitted for examination may consist of any one or any combination of these elements.

2.1. IMPLANTATION AND CHANGES IN THE ENDOMETRIUM IN PREGNANCY

While this is an extensive subject, a brief summary aids in the understanding of the changes which occur in the endometrium and which may be seen histologically.

2.1.1. The process of implantation.

The process of implantation begins on about the sixth day after conception. The blastocyst has developed trophoblastic buds and the primitive chorion has differentiated into cytotrophoblast and syncytiotrophoblast and has reached the uterine cavity. Trophoblastic invasion of the decidua begins as trophoblast grows from the cytotrophoblastic shell into uterine tissue, invading the interstitial tissues of the decidua and myometrium (Novak 1962). Some cytotrophoblast invades the distal segments of the spiral arteries, becoming endovascular. The endothelium of the intradecidual segments of the spiral arteries are replaced and there is loss of the musculo-elastic tissue of the media. This process is well established by the sixth week of gestation. A second wave of trophoblastic invasion occurs at 16 - 18 weeks.

It was noted by Pijenburg et al (1980) in their studies of the placental bed in hysterectomy specimens that trophoblastic invasion was accompanied by extensive decidual necrosis. It was thought that the obliquely orientated spiral arteries are breached by trophoblast to form new openings into the intervillous

space. The development of these new openings could result in altered blood flow patterns in the distal segments of the vessels as a consequence of which the widespread decidual necrosis occurs, giving the appearance of 'ghost' segments of spiral arteries in the necrotic areas.

The term 'intermediate trophoblast' was introduced to describe a type of trophoblast intermediate between syncytio-and cytotrophoblast with specific morphological, biochemical and functional features (Kurman 1984). Intermediate trophoblast is localised in the trophoblastic columns and placental bed and is thought to be of importance in implantation and establishment of the uteroplacental circulation (Wells 1988).

The physiological changes converting the spiral arteries to uteroplacental arteries are effected in the upper decidua by the action of endovascular and perivascular cytotrophoblast, whereas in the deeper decidua endovascular trophoblast is principally involved.

2.1.2. The endometrium of pregnancy

The growth of the endometrium starts in the proliferative phase and continues, in the absence of pregnancy, up to 3 or 4 days prior to menstruation when regression occurs. With fertilisation, endometrial regression does not occur. One or two days after implantation HCG secretion begins. Plasma progesterone rises and, as a result, the secretory mucosa is further stimulated to form the gestational endometrium. There is a marked increase in endometrial glandular secretions, accompanied by stromal oedema, decidualisation and vascular engorgement and

proliferation. There is an initial predecidual phase, and by the ninth day after implantation mature decidual cells are present (Shettles 1963).

Three types of decidual cells have been described in human pregnancy:

- 1) small, undifferentiated cells with scanty cytoplasm,
- 2) medium-sized cells rich in glycogen and lipids, and
- 3) cells with mottled cytoplasm and abundant ribosomes and mitochondria, a small nucleus and an undulating periphery surrounded by a membrane-like dense lamina.

Contained in the cells are amylase-resistant deposits or collagen inclusions which are thought to play a role in limiting trophoblastic invasion. The intensity of this phenomenon may be used to distinguish between a true decidua of pregnancy and the predecidual change in the secretory phase of the menstrual cycle or the pseudodecidua induced by prolonged progestagen therapy (Ferenczy 1974).

The decidua reaches its maximal height by the 17th day of gestation. Later, when the decidua basalis, capsularis and parietalis separate, and because the placenta grows so rapidly, destruction and remodelling occurs. This is associated with small necroses and polymorphonuclear infiltration.

Phloxine - tartrazine staining shows that most of the inflammatory cells contain phloxinophilic granules characteristic of endometrial granulocytes. These cells were originally called Kornchenzellen or 'K' cells and are now well recognised in human endometrium, particularly in the late secretory phase

(Bulmer 1987, Wells 1988). They increase as decidualisation progresses in early pregnancy. While the appearance of endometrial granulocytes does not depend on the presence of trophoblast, they tend to aggregate in areas where invasive trophoblast is found, particularly so in areas of maternal tissue degeneration where trophoblast invasion is heaviest. They may play a role in the complex immunological mechanisms of pregnancy but this has as yet not been established. Their presence may, however, be useful in diagnosing a pregnancy state in association with decidua, necrosis and haemorrhage when chorionic villi are not identified.

2.2. PATHOGENESIS OF ABORTION

The incidence of abortion is not easy to establish. Clinically recognisable spontaneous abortion occurs in between 10 and 15% of pregnancies. However, if the fate of all ova coming into contact with sperm is considered, then it has been estimated that only 30 - 40% of them result in births of more than 28 weeks gestation. The diagnosis of early pregnancy and its failure has been reviewed by Grudzinskas (1985). In a study of ova obtained from fertile patients Hertig indicated a theoretical abortion rate of 29%. He pointed out that there is an intrinsic defectiveness in about 40% of fertilised ova but that only approximately 12% would be sufficiently defective to result in clinical abortion. The incidence of early conceptual loss appeared to be greater in patients who were subfertile (Sharp 1986). A more recent prospective study (Miller 1980) of postimplantation pregnancy wastage revealed a pregnancy failure rate of 43%, only just over one fifth of pregnancies being clinically recognised as spontaneous abortions. It

must be accepted, therefore, that material submitted for pathological examination is highly selected and biased towards late abortions.

In South Africa, defining the incidence of spontaneous abortions is further confounded by the fact that, due to the current laws regarding termination of pregnancy, many criminal abortions are performed. These may present as incomplete abortions and the relevant history is often difficult to elicit. Recruitment strategies for studies on spontaneous abortion have always proved difficult and thus the incidence remains difficult to ascertain (Sweeney 1989).

2.2.1. Aetiology

The aetiology of spontaneous abortion is diverse. A brief discussion of the causes is documented below. (Table 1).

TABLE 1 : CAUSES OF ABORTION

1. Chromosomal abnormalities
 2. Anatomical abnormalities
 3. Infections
 4. Trauma
 5. Maternal disease
 6. Endocrine disorders
 7. Immunological factors
 8. Abnormal placentation
 9. Other
-

Of the above causes some are readily identified by studying the woman and her partner, while others are

best identified by studying the abortus directly (Stranz 1983, Rushton 1987). The evaluations are complementary.

Chromosomal abnormalities

Chromosomal abnormalities account for 50 to 60% of first trimester spontaneous abortions (Turnbull 1991, Rushton 1987). Using modern culture and chromosome binding techniques, the diagnosis can be accurately documented. The commonest abnormalities are trisomy, triploidy and monosomy. In 10% of cases there is a rearrangement of the parental chromosomes, e.g. a balanced translocation. Evaluation of the aborted material involves karyotyping, culture and gross and microscopic examination. In patients where an intact gestational sac is submitted for assessment, the following results were found by Kalousek (1987).

- 25% - no embryo (blighted ovum)
- 32% - incompletely formed embryo
- 18% - localised defects
- 25% - normal embryo

The first two are often associated with chromosomal abnormalities. In the majority of cases an intact gestational sac is not sent for examination and, in fact, a series by Houwert-De Jong (1990) showed that only 19% of samples had evidence of a fetus or fetal tissue present. This has led to studies on the placenta and certain morphological changes have been found to correlate with karyotypic abnormalities. While this appeared promising in that it would enable a diagnosis to be made on small amounts of material from curettage, the sensitivity and specificity were not sufficient to obviate the need for karyotyping (Novak 1988).

Anatomical abnormalities of the uterus

There is a definite but not inevitable association between uterine abnormalities and early pregnancy loss. Arcuate, subseptate and bicornuate uteri predispose to this as do submucous fibromyomata. Congenital or acquired cervical incompetence is a recognised cause of recurrent midtrimester abortions.

Infections

Infections have been implicated in some cases and the organisms involved include toxoplasma, listeria, brucella, chlamydia and mycoplasma as well as herpes simplex and cytomegalovirus (Turnbull 1991, Stirrat 1983).

Trauma

Trauma to the abdomen has been implicated in the causation of abortion (Hertig 1943) as has surgical trauma in patients requiring laparotomies for other intra-abdominal pathology.

Maternal disease

Many maternal diseases have been implicated in abortion although the evidence for such an association is not very convincing. These include hypertension, syphilis and chronic debilitation. Similarly, abortions have often been attributed to endocrine causes. The incidence of abortions seems to be increased in patients with diabetes and thyroid disease, particularly hypothyroidism. Deficient progesterone secretion in the luteal phase has also been implicated. This results in an abnormally developed endometrium and may disturb implantation of

the blastocyst. In patients falling pregnant within six months of discontinuing oral contraception who subsequently abort, a deficient secretory phase has been reported in 50% (Dallenbach-Hellweg 1981).

Immunological factors

Various immunological aspects have been considered in the aetiology of abortions, particularly when these are recurrent (Clark 1991, Stirrat 1983, Chaouat 1990). The most important mechanism in immune abortions relates to a lack of all major histocompatibility (HLA) antigens on villous trophoblast and the presence of Class 1, but absence of Class 2, antigens on non-villous trophoblast (Mowbray 1990). It has been postulated that trophoblast shares some antigens with maternal lymphocytes. Implantation and fetal development require maternal immunological recognition of trophoblast - lymphocyte - cross reactive (TLX) antigens. It has been suggested that the mother mounts a protective antibody response towards these TLX antigens which protects the trophoblast from immune attack against other closely associated antigens (McIntyre 1986).

Several workers have suggested that women who abort recurrently are more likely to share HLA antigens with their partners. They would then tend to produce a conceptus which also shares TLX antigens. This prevents the normal protective response to TLX antigens from occurring, allowing a damaging response against other closely associated antigens. McIntyre and Faulk (1986) divided aborters into primary and secondary aborters. Primary spontaneous aborters tend to share HLA antigens whereas secondary aborters manifest cytotoxic non-HLA dependent antibodies to the

husband's lymphocytes. These are antibodies to the TLX antigen. They have reported a 90% successful pregnancy outcome with immunotherapy in primary aborters but not in secondary aborters where they have had some success with heparin therapy. Possible suppressor cell deficiency may also be a factor (Clark 1987).

A few maternal autoimmune conditions cause pregnancy loss through the transplacental passage of maternal antibodies that act on the fetus through classic autoantibody-mediated mechanisms. These include congenital complete heart block associated with maternal systemic lupus erythematosus and mediated via anti-Rho antibodies. Also, some fetuses of mothers with autoimmune thrombocytopaenia develop thrombocytopaenia due to maternal antiplatelet antibodies crossing the placenta. Transfer of thyroid antibodies in patients with Grave's disease can also occur (Branch 1990).

Pregnancy loss is also associated with maternal autoantibodies that bind to negatively charged phospholipids. These are the antiphospholipid antibodies or lupus anticoagulant (Mowbray 1990, Gregorini 1986). They are associated with several clinical problems including thrombosis and appear to cause recurrent abortion in approximately 5% of cases. These are often late first or second trimester abortions. The aetiology appears to be a decidual vasculopathy involving the maternal spiral arterioles and resulting in uteroplacental insufficiency. The mechanism behind this is unknown but may be due to impaired prostacyclin production which mediates the interaction between migrating intravascular trophoblast and the uterine wall, a crucial event in normal placentation (Gregorini 1986).

Defective placentation

Defective placentation has been listed as a cause of abortion (Khong 1987). This is probably the end result of a variety of causative mechanisms, some of which have already been discussed. There is also some epidemiological evidence to suggest that cigarette smoking may be associated with spontaneous abortion. Scantier evidence exists of an association between gravidity, early age at menarche and alcohol consumption and abortion (Bocciolone 1989).

Numerous rarer causes exist and these include cord pathology, collagen diseases such as pseudoxanthoma elasticum and drug therapy (Viljoen 1987).

Some of these causative factors may be apparent histologically.

2.2.2. Mechanism of abortion

Regardless of the underlying aetiology, the precipitating cause of abortion is the regressive decidual change, necrosis and haemorrhage, and separation of the placenta.

If the embryo dies first, the placenta may survive for a long time and continue to produce hormones, particularly gonadotropin. In the decidua gonadotropin overstimulates the cells causing enlargement of the nuclei of the glandular epithelial cells. The intrauterine retention time depends on trophoblast viability (Chihara 1988). Inability of the trophoblast to maintain an adequate maternal blood supply either as a primary event or secondary to abnormal placentation results in abnormalities of the trophoblast which are evident to the pathologist. As trophoblast function further declines, the vascular

changes in the placental bed associated with pregnancy initially fail to progress and then regress leading to further trophoblastic failure, decidual necrosis and uterine irritability which eventually leads to expulsion of the fetus.

The detachment of abortion, unlike menstruation, starts with necrosis in the upper layer of the decidua. The placenta and decidua almost always involute completely. The degree and extent of their involution are dependent on how long the initiating haemorrhage lasted and on the cause of the abortion (Novak 1962). In infections the decidua usually involutes rapidly.

In early pregnancy the uterine attachments are tenuous and, in the course of labour, the fetal sac and decidua are usually extruded intact. Later in pregnancy, until about the fourteenth week, portions of the villi may be torn from the uterine wall in the course of labour, while some chorionic tissue remains adherent. The pathologic specimen is incomplete and fragmented and may only be obtained in full through curettage. In late abortion, expulsion of the fetus and placenta is often complete.

2.3. PATHOLOGY OF ABORTION

2.3.1. General Pathology

The three basic components of the early conceptus are decidua, placenta and embryo/ fetus. Their relative proportions vary from conception to term. In a 4-6 week pregnancy the decidual component predominates. During the next 10-12 weeks the placenta gains ascendancy and after this the fetus rapidly outgrows

the other components. Various classifications of the ovofetus have been devised. The standard classification is the Carnegie classification which relates to the presence or absence of villi, chorion, amnion and embryo and the nature of the embryo. A large proportion of the pathologic material derived from spontaneous abortions is incomplete and recovered from uterine curettage. The fragments of placental villi and/or decidual tissue from these are not classifiable into one of the major groups and a separate classification needs to be used, i.e. decidua without villi or villi only (Nesbitt 1962).

The placental villi found in curettings of spontaneous or induced abortions due to maternal causes are usually regular in shape and well preserved, although the decidua is shrunken or necrotic. Occasionally, however, the villi are necrotic or hyalinised. In these cases they lose their surrounding trophoblastic cells and lie embedded in coagulated blood and fibrin. Special stains are then needed to distinguish them from the surrounding fibrin and they appear hazy, giving rise to the name "ghost villi". Between these two extremes villi in various stages of degeneration may be seen. These must be differentiated from primarily malformed villi. (Fig. 1).

Various changes occur in the placenta and decidual plate in spontaneous abortions. The findings of necrosis, haemorrhage and thrombosis are common pathologic changes in these cases. There is often a degree of inflammation as well. Leukocytic infiltrations may be prominent only in areas of tissue destruction, or there may be diffuse inflammation with focal abscesses throughout the decidual plate. A distinct retroplacental haematoma may sometimes be evident.

FIGURE 1

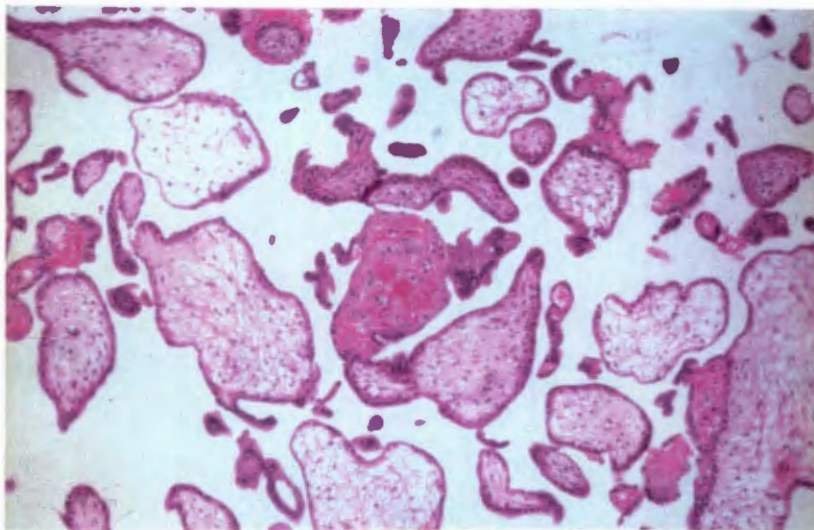


FIG. 1A
Chorionic villi

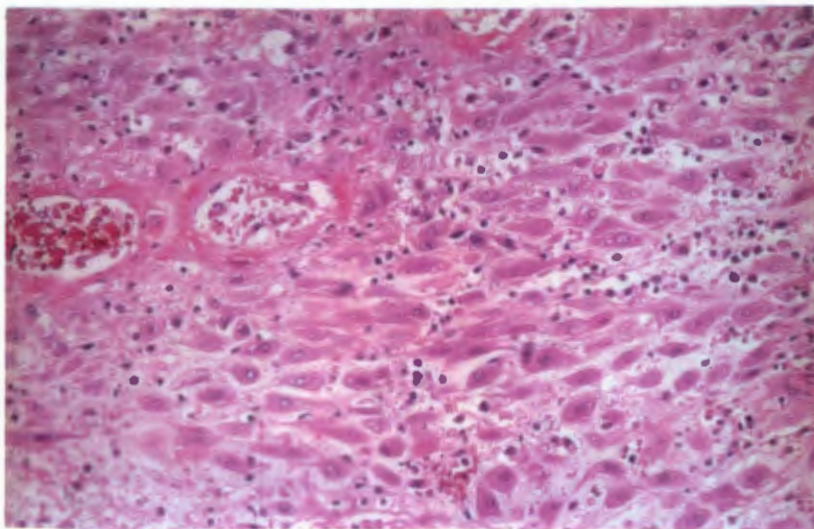


FIG. 1B
Decidual
Cells

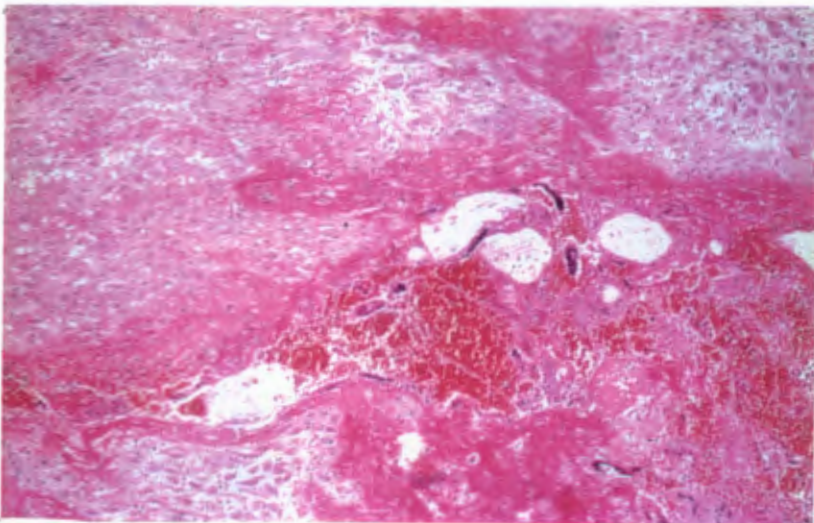


FIG. 1C
Necrotic Villi
Surrounded by
blood clot and
debris

While some of the changes in the placenta and decidua may be useful in ascertaining the cause of the abortion, many of them are degenerative in type and should not be regarded as causative.

2.3.2. The Arias - Stella phenomenon

The Arias-Stella phenomenon was first mentioned by Deelman in 1933, but more precisely described by Arias-Stella in 1954 under the title "atypical endometrial changes associated with the presence of chorionic tissue".

It was then thought that the presence of this reaction did not necessarily mean simultaneous co-existence of a pregnancy. Accumulated literature suggests that the change is a hormone dependent phenomenon, and this has been reproduced by injecting gonadotropin into the female rat. The basic characteristics of the change as elaborated by Arias-Stella are nuclear enlargement and some degree of secretory and/or proliferative activity in the epithelial cells. Two patterns are described. The first is a hypersecretory pattern. This is usually present in normal pregnancy, abortions or ectopic pregnancies. Distortion of the cells is emphasised when the involution and degeneration of an abortion takes place. It may, therefore, be confused with a degenerative or postinflammatory phenomenon. The second pattern is where the secretory effect is minimal and the proliferative activity intense. The nuclei are polypoid and gigantic and may be confused with carcinomas.

The presence of this phenomenon in abortions is usually focal and varies in intensity. There is a wide variability in the reported incidence of Arias-Stella phenomenon in abortions and ectopic pregnancies. This

depends partly on whether minor modalities are taken into account. With careful histological examination about 50% of spontaneous abortions should display the Arias-Stella phenomenon. Many investigators have been concerned with its association with ectopic pregnancy and this will be discussed later.

2.3.3. Hydropic degeneration of villi

Abnormalities of the placenta relate to the time at which embryogenesis was disturbed. If this occurs before establishment of the placental circulation in the villi, then the villi will be predominantly avascular and hydropic as the immature trophoblast continues to take up fluid (Ladefoged 1980). As the villi swell, the trophoblast becomes atrophic. When viewed under the microscope they appear as miniature molar villi, hence the term microscopic hydatidiform change.

If the embryonal circulation has already been established, then cessation of blood flow will result in stromal fibrosis and vascular obliteration. When this finding is diffuse, it is sometimes difficult to distinguish it from a hydatidiform mole. The significant finding in the latter condition is proliferation of the trophoblast rather than changes in the villous stroma. The villi also contain large cystic spaces.

In a study by Abaci (1968) 41,3% of spontaneous abortions had the hydropic changes mentioned above. In other studies the incidence of blighted ovum or anembryonic pregnancy has varied between 49 and 90%. This is important in that defective ovum development may be an important causative factor in abortions, and also that this condition must be differentiated from

gestational trophoblastic disease with which it has certain histological similarities. This condition has a slightly higher incidence of associated chromosomal abnormalities.

Hydropic villous degeneration has also been described with greater frequency in tubal pregnancies, suggesting that whatever retards the progress of the ovum through the tube, also results in abnormal placental formation (Pschera 1989, Emmrich 1981). In this study patients with blighted ova diagnosed ultrasonographically were excluded. However, a few were present where the diagnosis was made histologically.

2.4. DIAGNOSIS OF ABORTION ON CURETTINGS

The diagnosis of incomplete abortion is made by a combination of the history, clinical findings, previous documentation of a pregnancy either by pregnancy test or ultrasound and the gross and microscopic appearance of tissue expelled from the uterus. The expelled tissue may quite clearly be seen to be a fetus or gestational sac or placenta, or material may only be obtained at uterine curettage. Gestational age is of great importance in determining the nature of the curettings. As previously discussed, a very early pregnancy loss may consist mainly of decidua with very few other features evident.

Traditionally histological confirmation of the pregnancy has been regarded as necessary to be sure of the diagnosis. While occasionally fetal parts may be seen either macroscopically or microscopically, the more common situation is for only curettings to be available for examination. The presence of fetal parts, membranes, chorionic villi or trophoblast

confirms the presence of a recent intrauterine pregnancy.

There are, however, some pitfalls in establishing the histological diagnosis of abortion from curettings. In early abortions, failure of embryonal development and poor placental formation may result in most of the curettings yielding decidua only. In the absence of villi or fetal elements, the histological diagnosis of pregnancy or pregnancy-related conditions can be suggested from the presence of a number of findings:

- 1) viable or regressing decidua;
- 2) identification of remnants of Nitabuch's membrane;
- 3) postabortal cellular infiltration (endometritis) and stromal changes at implantation and non-implantation sites;
- 4) focal hyperplasia of smooth muscle in endometrial stroma;
- 5) atypical epithelial change in association with chorionic tissue (Arias-Stella phenomenon);
- 6) changes in the spiral arterioles. The frequency of these findings is shown in Table 2.

TABLE 2 : ENDOMETRIAL FINDINGS IN 100 CASES OF ABORTION

<u>FINDING</u>	<u>%</u>
Decidua	92
Spiral arteriolar changes	90
Arias-Stella phenomenon	88
"Endometritis"	74
Venous thrombosis	73
Nitabuch's membrane	32

These features were not specifically looked for in this study. The results confirm, however, the difficulties with diagnosis and the fact that a number of factors should be considered in association.

Where only decidua is present without any fetal elements, the diagnosis of intrauterine or extrauterine pregnancy may be made. Although this diagnosis cannot be definitive, in the appropriate clinical setting it may be made with a reasonable degree of certainty. It must be borne in mind that a positive finding of fetal elements represents absolute confirmation of a recent intrauterine pregnancy. However, absence of fetal elements may be due to a number of factors. Firstly, most of the pregnancy may already have aborted by the time that the curettage is performed. Secondly, all of the material is not sent for examination and, of the material that is examined, only a few sections are analysed. As these sections are very thin, they may not necessarily represent the features of the entire block of tissue. When it is felt that some of the features discussed above as representing an abortion have been seen, further examination of the sections is not made.

Other causes of decidua-like changes in the endometrium include the following : persistent corpus luteum, granulosa-cell tumours, other hormone producing ovarian carcinomas, progestagen therapy, mechanical stimulation, for example, with intrauterine contraceptive devices. It is important to know what type of decidua is present and what the likely cause is. Characteristics that may help in reaching a definitive diagnosis are listed in Table 3.

TABLE 3: SOURCE OF DECIDUA

	INTRAUTERINE PREGNANCY	ECTOPIC PREGNANCY	PROGESTAGENS	IUCD
Last menstrual period	> 4 wks ago	> 4 wks ago	> 4 wks ago	< 4 wks ago
Glands	High secretion Occ. A-S phen	High secretion Occ. A-S phen	atrophic	High secretion Occ A-S
Decidualisation	complete	complete	complete	focal
Inflammatory infiltrate	present	none	none	present
Fetal parts	often present	none	none	none

The above mentioned differentiating features exclude other causes of decidua-like change to a large extent. This cannot, however, be absolute.

2.5.DIAGNOSIS OF ECTOPIC PREGNANCY ON CURETTINGS

THE ENDOMETRIA ASSOCIATED WITH ECTOPIC PREGNANCIES

Considerable reliance has always been placed on the appearance of curettings in patients with suspected ectopic pregnancies. The presence of decidua without evidence of villi or fetal parts on histological examination has always been considered an important diagnostic feature.

Some of the features which may be helpful in distinguishing the decidua of abortion from that of extrauterine pregnancy are shown in Table 3. After the death of the fetus in an ectopic pregnancy, the decidua regresses. This usually progresses very slowly. Because of the absence of fetal parts, an inflammatory response in the endometrium is less common than with abortions.

In a study by O'Connor and Kurman (1988) various histological findings in the endometria of proven ectopic pregnancies and abortions were reviewed. 22% of women with the diagnosis of incomplete abortion had no villi on histological examination of their curettings. In order to determine which of these were

intrauterine and which were extrauterine, they examined various histological features while following the patients up clinically. Their findings were that intrauterine gestations demonstrated a significant increase in the size and luminal wall thickness of the vessels, as well as the presence of thrombosis. These features were, however, also present in a few of the ectopic pregnancies. They found changes of both acute and chronic inflammation to be present in equal numbers in intrauterine and ectopic gestations. Decidua was identified in 88.2% of the intrauterine pregnancies without villi and in 75% of the ectopic pregnancies. The single most useful histological feature in confirming the presence of an intrauterine pregnancy in curettings lacking chorionic villi was the finding of intermediate trophoblast associated with a fibrinoid matrix. This does, however, require special immunohistochemical stains.

Various authors have shown that a wide range of histological results may be present in the endometria of ectopic pregnancies. Decidua was found in only 19% of cases in one series with the remainder being either proliferative, secretory, regenerative or menstrual endometrium (Romney 1957). Bobeck (1957) found the incidence of decidua on curettings of ectopic pregnancies to be 46.9%. In all the other cases curettings showed endometrium.

The Arias-Stella phenomenon may be present, but is by no means diagnostic of an ectopic pregnancy. It occurs also in abortions and in normal full term pregnancies. Some authors quote higher incidences in ectopic pregnancies. However, as the change is focal, the incidence varies greatly depending on the abundance of the curettings and the closeness of scrutiny.

Thus, while the presence of villi or trophoblast on histological examination of curettings excludes an ectopic pregnancy, the more common finding of decidua or endometrium without villi is more frequently present in other conditions, such as incomplete abortions.

2.6. CONDITIONS MIMICKING ABORTIONS

Spontaneous abortion is one of the commonest admission diagnoses to gynaecological wards throughout the world. Mola (1988) reported that 1 in 10 patients with this diagnosis in Papua New Guinea were in fact suffering from dysfunctional uterine bleeding.

If clinical features are unhelpful in differentiating between the two conditions, histological examination of the curettings may provide the diagnosis. In cases of dysfunctional bleeding the histology of the curettings is commonly reported as proliferative endometrium or hyperplasia. The differentiation between abortions and dysfunctional uterine bleeding is of importance in patients who are having repeated periods of amenorrhoea followed by heavy bleeding and may think that they are having recurrent abortions. Therefore, in patients with histories or clinical findings atypical of incomplete abortion, curettings should be sent to confirm the diagnosis.

The other condition which may mimic a spontaneous abortion clinically and histologically is hormone therapy with progestagens. This produces a state of pseudodecidualisation in the endometrium. The features distinguishing this from true decidua of pregnancy are documented in Table 3.

Ectopic pregnancies may also present as abortions and

this has already been discussed.

2.7. TROPHOBLASTIC DISEASE

The term 'trophoblastic disease' encompasses a number of conditions: hydatidiform mole, invasive mole, metastasising mole, choriocarcinoma and placental site trophoblastic tumour. Hydatidiform mole may be partial, coexisting with a fetus, or complete. It consists macroscopically of large, translucent villi. The villi are swollen and avascular and there is trophoblastic proliferation. The feature distinguishing a true hydatidiform mole from an abortion with hydropic change is the presence of trophoblastic proliferation. In all probability a spectrum of stromal transformation exists, from simple hydrops to fully developed hydatidiform change.

Choriocarcinoma is characteristically red, spongy and friable tissue protruding into the uterine cavity or buried in the myometrium. Microscopically, the tumour is composed of sheets of atypical trophoblast, primitive in appearance with syncytiotrophoblast forming a thin lining over cords of cytotrophoblast. An important criterion for the diagnosis of choriocarcinoma is the absence of chorionic villi (Ober 1987).

The placental site trophoblastic tumour is a tumour of intermediate trophoblast. Intermediate trophoblast is a constituent of villous trophoblast but also exists as extravillous trophoblast (Young 1988).

There are certain pitfalls in the histological interpretation of proliferative lesions of the gestational trophoblast. Two common conditions share morphologic features with the major lesions of

gestational trophoblast. The hydropic abortus may resemble hydatidiform mole and the implantation site in early pregnancy and later spontaneous abortion may suggest either choriocarcinoma or placental site trophoblastic tumour (Driscoll 1987). The features distinguishing blighted ovum from hydatidiform mole have already been discussed.

Placental site trophoblastic tumour must be distinguished from benign placental nodule and exaggerated placental reaction. Intermediate trophoblast is sometimes difficult to distinguish from decidual cells and smooth muscle cells at the implantation site. Immunohistochemical staining with human placental lactogen (HPL) may be useful in this regard. Infiltration of the endometrium and invasion of the uterine vessels usually regresses rapidly after delivery or abortion. The unusual persistence of this placental site reaction may occur but in most cases is self-limiting. Rarely, this phenomenon is abnormally extensive with local myometrial infiltration. Metastases may occur. The diagnosis of this condition is difficult and, if any doubt exists, patients should be followed up with human chorionic gonadotropin (HCG) estimations. It has also been suggested that repeat curettage be performed to attempt to confirm the diagnosis (Young 1988).

The diagnosis of choriocarcinoma on curettings is more difficult. The finding of villi in a postmolar curetting is an indication that choriocarcinoma has not developed at that time, but invasive mole cannot be excluded. Interpretation of curettings after a molar pregnancy should be undertaken with caution. Before accepting a curetting as diagnostic of choriocarcinoma, all the histological criteria particularly invasion by trophoblast and absence of

chorionic villi, must be fulfilled. Placental site reaction is the commonest cause of diagnostic difficulty and the appearances are often confused with that of choriocarcinoma.

Uterine curettings must be carefully evaluated for these conditions in all cases. The incidence of unsuspected gestational trophoblastic disease diagnosed for the first time on histological examination is very low.

3. LITERATURE REVIEW

Traditionally all curettings from abortions are sent for histological examination , the purpose of this being:

- a) to confirm the presence of a recent intrauterine pregnancy
- b) to exclude gestational trophoblastic disease
- c) to exclude other conditions mimicking abortions, particularly ectopic pregnancy.

Many authors (Jeffcoate 1975, Novak 1962) state that histological examination is obligatory for these reasons.

Other reasons supporting routine histological examination are that the developmental state of the abortus may be used as a predictor of future pregnancy outcome and may thus contribute to management of subsequent pregnancies (Rushton 1981). This applies particularly in the case where a blighted ovum or hydropic villous degeneration is detected. While this may be a normal finding in placentae of early abortions (Ladefoged 1980, Joupilla 1980), a correlation has been demonstrated between chromosomal abnormalities in the aborted material and severe hydropic degeneration of the villi. While the diagnosis of blighted ovum has also been associated with chromosomal abnormalities, this diagnosis is more commonly made on ultrasound examination than on routine histological examination of specimens from spontaneous abortions (Joupilla 1980). Morphological changes in the placenta have been correlated with karyotypic abnormalities (Novak 1962, Rushton 1987, Houwert- De Jong 1990) with the suggestive features being villous scalloping with trophoblastic invagination. While certain histological features may

be suggestive of abnormal karyotype, the findings are not specific enough to obviate the need for karyotyping in the individual case (Novak 1988).

Lesions responsible for the expulsion of the fetus, such as retroplacental haemorrhage or infection, may be ascertained histologically, but these may equally be diagnosed clinically.

A further reason to support the argument in favour of routine histology is the contribution to our understanding of pathological processes responsible for miscarriage or early fetal death as well as later fetal demise (Imai 1988). Conditions such as pre-eclampsia and intrauterine growth retardation have specific histological features (Rushton 1987, Shen-Schwartz 1989). These, however, require special methods of histological examination and are probably of more use in pregnancies beyond the second trimester.

Epidemiological studies of congenital malformations would help to monitor the impact of environmental teratogens. It is not practical, however, to conduct such detailed histological examinations on all abortion material.

In considering the prime reason for routine histological examination, namely to confirm a recent pregnancy, the following facts should be noted.

The confirmation of pregnancy depends on the finding of fetal parts, chorionic villi or trophoblast histologically. However, by the nature of the early pregnancy and abortion processes these features may not be present. In the first 4-6 weeks of pregnancy the decidual component predominates and thus in early abortions the majority of curettings will consist of

decidua only (Rushton 1987, Nesbitt 1962, Joupilla 1980, Houwert-De Jong 1990). In one series (Hertig 1943) a fetus or fetal tissue was detected in 50% of cases and in another in only 19% of cases (Houwert - De Jong 1990). A large proportion of the material recovered from spontaneous abortions is incomplete and is recovered by uterine curettage. It is common to find only fragments of villi or decidua and certain curettings will show only old, haemorrhagic, necrotic, inflamed tissue without villi which is hardly discernible as decidua. This is more common in cases of septic abortion.

The traditional management of curettage for all abortions has been questioned. This approach is based on the assumption that residual trophoblastic tissue may prolong and intensify uterine bleeding and may facilitate endometrial infection and later promote the formation of intrauterine adhesions with subsequent menstrual disturbances and infertility.

A study to assess the frequency of residual trophoblastic tissue in curettage specimens obtained from women with spontaneous first trimester abortions, found that in only 12,6% of cases were villi present histologically (Schiff 1990). They found that the predictive features for the presence of residual trophoblast were a human chorionic gonadotropin subunit of greater than 500 mIU/ ml (Hay 1988), intrauterine tissue demonstrated ultrasonographically and active bleeding as well as higher gestational age. It was suggested that, using these parameters, the presence of villi could be predicted with a high sensitivity and about 60% of curettage procedures might be avoided.

Lindahl and Ahlgren (1986) found that of 272 patients

with clinical spontaneous abortions, 80,5% had chorionic villi identified by either macroscopic appearance, histology or both. The macroscopic appearance of villi was recorded by the gynaecologist after curettings were examined in saline. Villi were identified in 50%. The macroscopic and histological appearances correlated in 46% of cases. A further 30% were diagnosed histologically but not macroscopically. In 3,3% the finding of villi macroscopically was not confirmed histologically.

The 1983 United States Supreme Court ruling that tissue from therapeutic abortions should all be examined by a pathologist was supported by the results of a study of 13 477 cases from therapeutic abortions, where it was found that 98,7% had routine confirmation of the pregnancy (Kiel 1986). Of the remainder, 60% had deciduoid appearance suggestive of but not diagnostic of pregnancy, 39,5% were not diagnostic of pregnancy and 1% showed trophoblastic disease. In a subgroup of patients with non-routine reports, 28% had a problem warranting further care for ectopic pregnancy or trophoblastic disease or retained placental tissue. The conclusion was that a small percentage of patients received benefit from routine histological examination.

The second main reason for performing routine histological examination is to exclude gestational trophoblastic disease. The incidence of gestational trophoblastic disease (GTD) varies greatly from country to country and the incidence is thus difficult to define. It is generally accepted that the incidence is about ten times higher in the Far East than in the United States of America with the incidence of benign hydatidiform mole being 1:82 in Taiwan as opposed to 1:1 500 to 2 000 in the United States of America

(Bloch 1984). The incidence in South Africa lies between these figures.

The incidence of molar change is highest in blighted ova with 20 - 40% of abortions being affected (Rushton 1981). Studies have shown that the majority of blighted ova are diagnosed by ultrasound examination rather than a chance finding at histology (Joupilla 1980) and these specimens should all be sent for histological examination when the uterine evacuation is performed.

Because of the malignant potential of this disease, care in the examination of specimens has always been emphasised. The macroscopic appearance of hydropic villi usually indicates either a blighted ovum or hydatidiform mole. This appearance, however, is not always present in cases of GTD. The finding of GTD on routine histology of abortion curettings is low. In one study the only case diagnosed in 2 533 terminations of pregnancy was diagnosed by the macroscopic appearance (Tangtrakul 1984). In a further study of 13 477 cases of therapeutic termination of pregnancy where routine histological examination was undertaken, the incidence of hydatidiform mole was 0,015%. No comment was made as to whether these cases were able to be diagnosed macroscopically or not (Kiel 1986). A case was reported where a hydatidiform mole was missed following a therapeutic termination of pregnancy by suction evacuation of the uterus (DeCherney 1971). This method of evacuation is commonly employed for termination of pregnancies rather than curettage of retained products as in incomplete abortions. As the curettings are distorted by the suction apparatus and often not available for close inspection as they are deposited directly into a sealed receptacle, it is difficult to assess the

macroscopic appearance of the tissue removed. This is not the case with evacuations of retained products of spontaneous abortions.

The accuracy of diagnosis of choriocarcinoma from uterine curettings is still debated (Elston 1972) and this diagnosis is best made on the basis of raised HCG levels. The interpretation of curettings in the presence of a recent hydatidiform mole is difficult and this may also be the case following a spontaneous abortion where a placental site reaction may be mistaken for trophoblastic invasion (Driscoll 1972).

The final reason for suggesting that routine histological examination be carried out on all abortion specimens, is to exclude other conditions mimicking abortions. The two main conditions in this category are dysfunctional uterine bleeding and ectopic gestation. Dysfunctional bleeding is often confused with spontaneous abortion. Mola (1988) reported that 1 in 10 patients with this diagnosis in Papua New Guinea were in fact suffering from dysfunctional uterine bleeding. The diagnostic problem stems from the fact that both spontaneous abortion and dysfunctional uterine bleeding present with a period of amenorrhoea followed by heavy vaginal bleeding. The definitive signs which prove that an episode of heavy bleeding is an abortion are:-

- 1) If a visible fetus or embryo is passed
 - 2) If an ultrasound scan before the onset of bleeding showed the presence of a viable fetus
 - 3) If a definite membrane is seen at the time of evacuation of the uterus
 - 4) If a serum or urine pregnancy test is positive.
- This depends, however, on the accuracy of the test, and it is often difficult to obtain an

uncontaminated specimen in the presence of heavy bleeding.

In the absence of these findings histological examination of the curettings may provide the diagnosis. In cases of dysfunctional bleeding the histology of the curettings is commonly reported as proliferative endometrium or hyperplasia. The differentiation between abortions and dysfunctional uterine bleeding is of importance in patients who are having repeated periods of amenorrhoea followed by heavy bleeding and may think that they are having recurrent abortions. It is also important to define whether the cause is dysfunctional bleeding and to treat appropriately if this is the case. Therefore, in patients with histories or clinical findings atypical of incomplete abortion, curettings should be sent to confirm the diagnosis. There is usually little problem in distinguishing between the two conditions histologically.

Of more importance in terms of morbidity and mortality to the patient, however, is missing the diagnosis of an ectopic pregnancy. With the rising incidence of ectopic pregnancy (Hemminki 1987) it is important to ascertain whether histological examination of abortion specimens aids in earlier diagnosis.

Traditionally, the absence of fetal parts or villi on histological examination has been considered suggestive of ectopic pregnancy (Novak 1968, Jeffcoate 1975). Schafi (1988) reported seven cases where histology failed to confirm the presence of an intrauterine pregnancy which later presented as ectopic pregnancies.

Certain histological appearances of the endometrium

have been regarded as virtually diagnostic of extrauterine pregnancy. These include the presence of decidua without villi, and the Arias-Stella phenomenon.

It has already been noted that many spontaneous abortions will reveal decidua only at histological examination. The Arias-Stella phenomenon may be present in ectopic pregnancies but is by no means diagnostic. It occurs also in abortions and in normal term pregnancies (Arias-Stella 1974). Some authors quote higher incidences in ectopic pregnancies. However, as the change is focal, the incidence varies greatly depending on the abundance of the curettings and the closeness of scrutiny.

It was first observed by Boehmerus in 1752 that a decidual lining was formed in the uterus of extrauterine gestations. In order to investigate the conditions which co-exist with endometrium showing decidual reaction without the presence of villi, Bobeck (1957) reviewed a number of patients with this finding. The results are shown below :

Ectopic pregnancy (confirmed) :	17,2%
Suspected ectopic pregnancy (no operation) :	3,3%
Incomplete abortion :	28,7%
Complete abortion :	12,3%
Dysfunctional bleeding :	32,0%
Other :	6,5%

Various authors have shown that a wide range of histological results may be present. Decidua was found in only 19% of cases in one series (Romney 1950) with the remainder being either proliferative, secretory, regenerative or menstrual endometrium. Bobeck (1957) found the incidence of decidua in curettings from

ectopic pregnancies to be 46,9%. In all the other cases curettings showed endometrium. Information of better value is obtained from spontaneously shed tissue and from tissue obtained from curettage where bleeding has been slight. The heavier the bleeding and the longer its duration, the slighter the chance of finding decidua. Thus, where the pregnancy has died or been disrupted, decidua is not usually present. Ollendorff (1987) showed similar results in that only 22,6% of patients with ectopic pregnancies had decidua at histology, while 58,4% had either proliferative or secretory endometrium.

A further study (Lindahl 1986) showed that villi could be identified in 80% of clinically diagnosed spontaneous abortions and, of the remaining 20% where intrauterine pregnancy was not confirmed, one third proved to have an ectopic pregnancy.

The review of the literature shows varied opinions on the different aspects of the value of routine histological examination. The present study is designed to extend this evaluation.

4. AIMS OF THE STUDY

The purpose of this study was to ascertain whether, in first and second trimester abortions, the clinical diagnosis together with the macroscopic appearance of the curettings provided the correct diagnosis, and that histological examination of the curettings was therefore only necessary when the clinical diagnosis was uncertain and/or the curettings appeared atypical.

To this end it was attempted to disprove the null hypothesis which, in this case, may be stated as follows:-

In abortions the macroscopic appearance of the uterine curettings does not correlate with the histological diagnosis.

5. SUBJECTS AND METHODS

5.1. PATIENT RECRUITMENT

All patients presenting to the Gynaecology Department of the Groote Schuur Hospital in Cape Town during the period from the 1st February 1988 to the 31st December 1988 with clinically diagnosed or suspected incomplete abortions were included in the study.

Exclusion criteria:

- a) patients undergoing re-evacuations
- b) ultrasonically diagnosed gestational trophoblastic disease
- c) evacuations performed at the same time as laparotomies for proven ectopic pregnancies, i.e. that group of patients who were thought to have incomplete abortions but at the time of evacuation of the uterus, a suspicion of an ectopic pregnancy was raised, for example by the absence of curettings or the detection of an adnexal mass. In these cases a laparotomy was immediately performed, and the histology result thus did not influence the diagnosis or clinical management of the patient
- d) missed abortions or blighted ova diagnosed by ultrasound.

5.2. METHODS

These patients all underwent routine evacuation of the uterus under general anaesthesia. The perineal area was cleaned with disinfectant solution and the procedure performed under sterile conditions. In most cases the cervix was sufficiently dilated to permit the introduction of sponge holding forceps to remove larger fragments of tissue. If the cervix was

insufficiently dilated to allow this, Hegar dilators were used to achieve a suitable degree of dilatation. As much tissue as possible was removed with the sponge holding forceps and the uterine cavity was then curetted, using either a blunt or sharp curette. Syntocinon was given during the procedure to achieve uterine contraction and promote expulsion of any tissue fragments.

Specimens were sent for histological examination to the Department of Histopathology at the University of Cape Town. When copious amounts of tissue were obtained, representative specimens were sent. Where only small amounts of curettings were obtained, these were all sent for histological examination. Specimens were placed in formalin solution immediately after the evacuation.

At the time of the evacuation of the uterus, the clinical diagnosis and the macroscopic appearance of the curettings obtained, were recorded. A standardised form was used for this purpose (Fig. 2).

FIGURE 2

GROOTE SCHUUR HOSPITAL
DEPARTMENT OF GYNAECOLOGY

OPERATION.....	FIRM.....
NAME.....	WARD.....
FOLDER NO.....	DATE.....
SURGEON.....	ANAESTHETIST.....

ABORTION FORM

<u>DIAGNOSIS</u> (clinical):	Pregnosticon: +ve	-ve
Incomplete abortion	Missed abortion	
Trophoblastic disease	Other	Specify.....

<u>E.U.A.</u>	Vulva and vagina
	Cervix
	Uterus
	Adnexa

<u>APPEARANCE OF CURETTINGS</u>	POC	DECIDUA
TROPHOBLASTIC TISSUE	BLOOD CLOT	OTHER
		Specify.....

PROCEDURE: Retained products removed digitally & with
Ovum forceps

Uterine cavity curetted

Curetings: Scanty/profuse
Blood loss Syntocinon IV..
Sent for histology

ADDITIONAL NOTES

M.O.

5.3. MACROSCOPIC APPEARANCE

The macroscopic appearance recorded was the naked eye appearance of the curettings as observed by the registrar performing the uterine evacuation. This was divided into the following categories:-

Products of conception (POC)

Decidua

Endometrium

Trophoblastic tissue

Blood clot

Other

Where fetal parts, membranes, umbilical cord or placenta were present, or tissue fragments with the appearances of the above, this was recorded as products of conception (POC). The most common finding in this category was of profuse, fleshy curettings which were pale pink and had a firm consistency.

The diagnosis of decidua was recorded when no obvious fetal or placental remnants were noted, but profuse, fleshy curettings were obtained which were thought to differ from non-pregnant endometrium.

The diagnosis of possible gestational trophoblastic disease was recorded in most instances when hydropic villi were present, abnormal trophoblastic proliferation being difficult to distinguish macroscopically.

Endometrium implied the presence of non-pregnant curettings and blood clot that there were no other curettings at all.

The category 'other' was reserved for appearances

which did not fit into any of the other categories.

5.4. HISTOLOGICAL EXAMINATION

A significant part of this investigation is based on the results of the histological examination of microscopic slides made from the curettings sent to the Pathology Laboratory at the Medical School of the University of Cape Town.

In theatre all or selected parts of the curettings were placed in jars containing BUFFERED FORMALIN 10% pH7 to fix the tissue. This was then submitted to the Pathology Laboratory for histological examination.

5.4.1. Preparation of tissue

In the case of abortion specimens the entire specimen was not usually examined, but rather representative specimens were taken by the medical technologist for processing. As decidua has a fleshy appearance, there may have been a natural tendency to select these tissues for examination.

Tissue was dehydrated by passing it through graded alcohols. It was then impregnated with Xylol and paraffin wax and then embedded in paraffin wax.

5.4.2. Preparation of sections

Sections of 4-7 microns were cut from the paraffin blocks by a microtome and fixed onto slides. The sections cut from the wax blocks are very thin and may not represent all the features in the rest of the block. Where indicated, more sections would be cut to minimise the chances of missing important features.

The slides were stained by the HAEMATOXYLIN AND EOSIN METHOD. Haematoxylin is obtained commercially as Harris's Haematoxylin. Eosin consists of 1% Eosin and 0,5% Phloxine. The result of this stain was that the nuclei stain blue while the cytoplasm stains pink.

The slides were mounted and then examined microscopically by a pathologist and reported on.

These specimens were all processed as part of the routine workload of the Department of Histology. They were examined by pathology registrars or consultants who were not aware of the study and thus no special attention was applied to the specimens. The reports were thus representative of the general reporting procedure of the department.

5.4.3. Reporting

Reports were made on a pre-formatted form as one of the following:-

Products of conception (POC)

Decidua compatible with a recent pregnancy

Hypersecretory endometrium compatible with a recent pregnancy

Extravillous trophoblast. While this may be a placental site reaction, gestational trophoblastic disease cannot be excluded. Follow-up beta-HCG recommended

Hydropic villi consistent with blighted ovum

Endometrium - proliferative/ secretory

Blood clot only

Hydatidiform mole

For the purposes of this study, the above reports were condensed into the following categories:-

POC.

Decidua. This includes reports of hypersecretory endometrium

Endometrium

Extravillous trophoblast

Trophoblastic tissue

Blood clot

Other. Blighted ova have been included in this category.

The categories are thus the same for the macroscopic and histological appearances, except for the additional category of extravillous trophoblast, which is a histological finding only.

POC implies the presence of an embryo, gestational sac, membranes or placenta or, if fragmented curettings only are examined, the presence of chorionic villi. If there is doubt and it is thought that defining the presence of chorionic villi is essential, then special stains are used. This, however, is not done routinely.

Decidua is distinguished from endometrium in that the cells are plump and filled with cytoplasm. Collagen inclusions are often present and may distinguish between true decidua and the pseudodecidua associated with prolonged progestagen therapy.

The report of 'extravillous trophoblast' is made when trophoblastic tissue is seen outside the placental villi. This occurs normally at the placental site but, as this is difficult to identify in fragmented curettings, it is recommended that the patient be followed up with HCG estimations to be sure that gestational trophoblastic disease is not missed.

The other categories are self explanatory.

6. RESULTS

During the study period 1 513 consecutive patients undergoing evacuation of the uterus for incomplete abortions, were studied. Of these, 49 patients were excluded because of inadequately completed forms, lost specimens or lost histology reports. The remaining 1 464 patients and their results were analysed. The patients were initially assessed as having incomplete abortions and underwent uterine evacuation. The diagnosis recorded was that made at the time of evacuation and may have been influenced by the findings at examination under anaesthetic and by the nature of the curettings obtained.

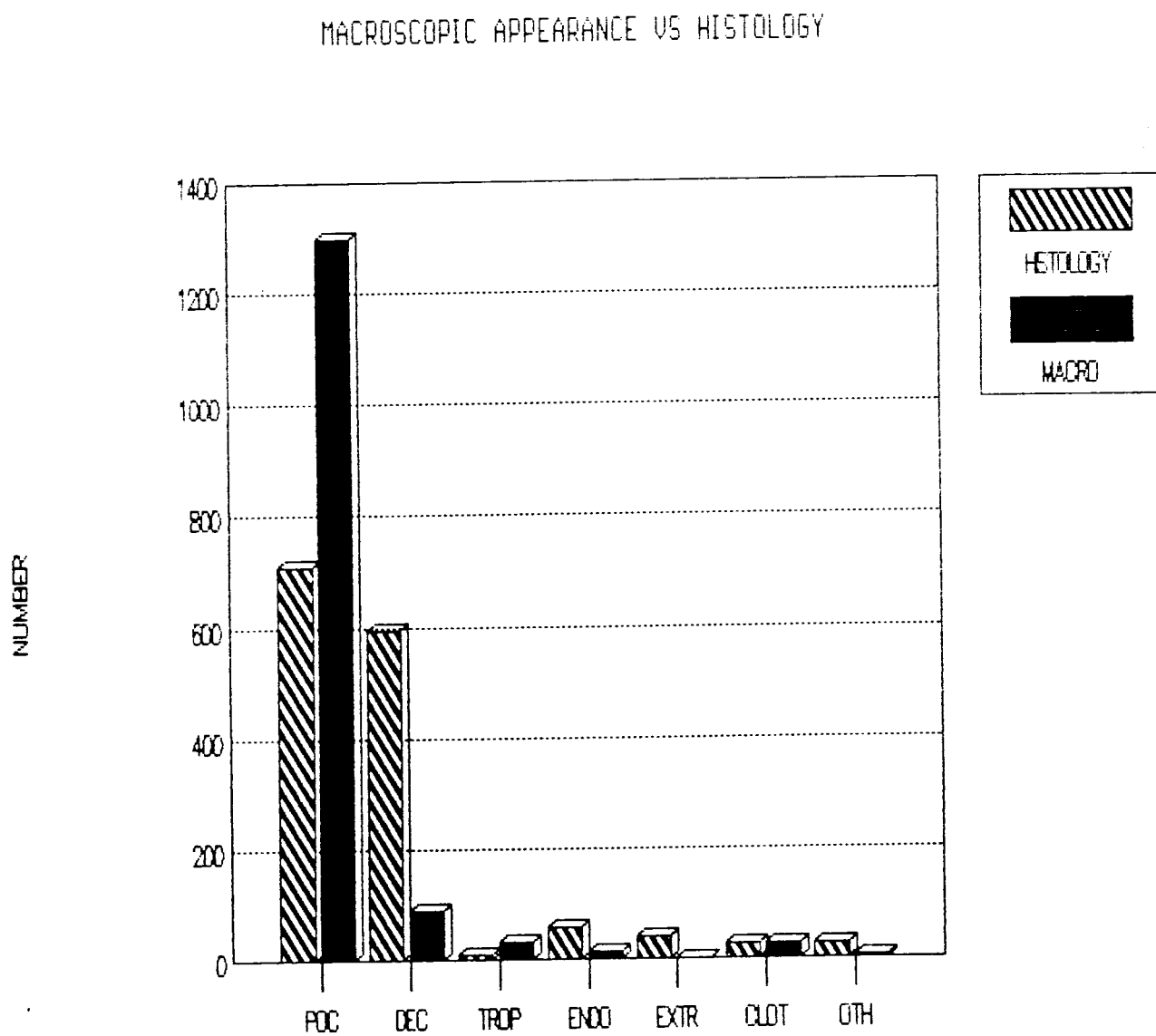
Thus, of the 1 464 patients, 1 394 had the diagnosis of incomplete abortion recorded. The remaining 70 patients had other diagnoses. These details are shown in Table 4.

TABLE 4. Clinical diagnosis

<u>DIAGNOSIS</u>	<u>NO. OF PATIENTS</u>	<u>%</u>
Incomplete abortion (ICA)	1394	95,2%
Trophoblastic disease	18	}
Complete abortion	16	}
Possible ectopic	9	} 4,8%
Dysfunctional uterine bleeding/ICA	12	}
Missed abortion/ ICA	2	}
No diagnosis	13	}

95,2% of patients were diagnosed as having incomplete abortions and 4,8% had other diagnoses recorded. In the latter group, doubt was expressed in a number of cases as to whether the diagnosis was correct and incomplete abortion was still considered. The

FIGURE 3



macroscopic appearance of the curettings was recorded.

This was later compared with the histological appearance. Fig. 3 shows the distribution of the various categories. It will be seen that on macroscopic appearance the majority of results were products of conception (POC). Histologically the majority were either POC or decidua. The other categories were represented by much smaller numbers. Table 5 shows the correlation between macroscopic and histological diagnoses.

TABLE 5: Macroscopic appearance vs Histology

HISTOLOGY	MACROSCOPIC APPEARANCE					
	POC	DECIDUA	TROPH.	ENDO	CLOT	OTHER
POC	679	16	10	0	2	0
DECIDUA	533	44	7	4	7	1
TROPH.	0	0	6	0	0	1
ENDO	26	17	2	8	6	0
EXTRAVILLOUS	34	5	1	0	1	0
CLOT	13	6	0	2	7	0
OTHER	13	2	5	0	3	3

The numbers in the clinical diagnosis table (Table 4) differ from those in Table 5 because, where there was a degree of uncertainty, a macroscopic appearance, which did not necessarily correspond to the clinical diagnosis, was sometimes recorded.

In 1 272 patients (86,9%) there was a correct correlation between the macroscopic and histological appearance which was compatible with an incomplete abortion. 679 of these patients (46,4%) had POC macroscopically and histologically, while 533 (36,4%) had POC macroscopically and decidua on histological

examination. In this study POC and decidua have both been taken as implying the presence of a recent pregnancy (see discussion).

Statistical studies

The histological diagnosis is used as the gold standard for making the diagnosis of abortion. This has limitations in that all tissue may not be examined and the relevant tissue may already have been aborted. It can be assumed, however, that a positive diagnosis of POC or decidua confirms the presence of a recent pregnancy, but a negative diagnosis does not necessarily exclude it.

The macroscopic diagnosis is thus compared with the histological one and the sensitivity, specificity and predictive value of the test calculated.

Sensitivity	: 96,6%
Specificity	: 19,3%
Positive predictive value	: 91,6%
Negative predictive value	: 40,1%
Accuracy	: 89%

Using the Kappa statistic (k) which is a measure of agreement, $k = 0,26$. The 95% confidence limits are as follows :

$k \pm 1,96 \text{ se}(k)$, where se = standard error

Thus 95% confidence intervals = 0,16; 0,36.

These results disprove the null hypothesis.

Trophoblastic disease

15 patients were diagnosed as having molar pregnancies in the period of the study. Of these 8 had the

diagnosis made at ultrasound examination and confirmed histologically.

Trophoblastic disease was diagnosed on macroscopic appearance in 31 patients, but only confirmed histologically in 7 cases. Thus there were 24 false positives and no false negatives.

In the group with reports of extravillous trophoblast there were 41 patients. They were asked to return for HCG estimations.

Beta -HCG negative	: 10
Beta -HCG 5,8 (marginally raised)	: 1
Defaulted follow-up	: 30

Of the patients who defaulted follow-up, one presented two months later with bleeding. Beta - HCG at this stage was 37 000 mIU/ml and she received chemotherapy.

Ectopic pregnancies

There were 5 patients with confirmed ectopic pregnancies. Only two of these were suspected pre-operatively or at evacuation of the uterus. the suspicion was not strong enough to proceed to laparotomy at the time and instead histology was awaited. The remaining 3 patients were thought to have incomplete abortions. The histology of the curettings in these patients with ectopic pregnancies was as follows:

Endometrium	: 2
Decidua	: 1
'Insufficient'	: 2

9 patients had ectopic pregnancies suspected. Of these

only 2 were confirmed. In the remaining 7 patients, histological examination of the curettings was as follows:

Endometrium : 4
Decidua : 2
No curettings : 1

These patients had either complete abortions or dysfunctional uterine bleeding.

In the 70 patients where the diagnosis was uncertain and a diagnosis other than incomplete abortion was considered, the distribution of results is different. These are shown in Table 6.

TABLE 6.

DIAGNOSIS	MACROSCOPIC APPEARANCE				HISTOLOGY			
	POC	DEC	TROP	ENDO/CLOT OTHER	POC	DEC	TROP	ENDO/CLOT OTHER
? ectopic	2	0	0	7	0	3	0	6
Troph. dis.	5	1	11	1	4	5	6	3
Complete	3	5	0	8	1	4	0	11
DUB	0	2	0	10	0	1	0	11
Missed ab.	0	2	0	0	0	0	0	2
No diagnosis	10	1	1	1	5	5	0	3

A small percentage of patients had histological reports of blighted ovum or hydropic abortion. These were not included as POC but listed in the category "other". (See introduction).

7. DISCUSSION

The purpose of this study was to evaluate the need for routine histological examination of uterine curettings from first and second trimester abortions, and also to assess an alternative way of diagnosing abortion accurately, without missing the diagnosis of related conditions.

The study will be discussed with reference to the three traditionally accepted reasons for histological examination of all curettings, viz.:

- a) to confirm the presence of an intrauterine pregnancy
- b) to exclude gestational trophoblastic disease
- c) to exclude other conditions such as ectopic pregnancy

(a) Diagnosis of intrauterine pregnancy

In order to confirm the presence of an intrauterine pregnancy, fetal parts, chorionic villi or trophoblast must be identified histologically. While the positive finding of any of these features definitely confirms the presence of a recent pregnancy, their absence does not exclude the diagnosis, for the reasons previously discussed.

In this study only 707 of the 1 464 patients (48,3%) had the histological diagnosis of products of conception (POC). In 95,2% of patients, the clinical diagnosis was unequivocally stated as incomplete abortion.

Only 5 patients had known ectopic pregnancies and 56 (4%) may have had dysfunctional uterine bleeding on the basis of the endometrial histology.

A further 28 had only blood clot at curettage. Some of these may have had complete abortions and others may have had dysfunctional bleeding.

The 26 patients with histology classified as 'other' had a variety of histological results including blighted ovum, cystic hyperplasia and other endometrial changes.

After excluding all these groups there still remain 627 patients with clinically diagnosed incomplete abortions with nothing to suggest any other diagnosis, where the histological examination does not show POC and therefore cannot conclusively confirm the presence of a recent intrauterine pregnancy. These results are in keeping with other studies where the finding of fetal parts or villi in abortion specimens was less than 50% (Hertig 1983, Houwert-De Jong 1990).

From Table 5 it can be seen that on macroscopic appearance the majority of the results are POC. In 1 298 patients (88,7%) this diagnosis was recorded macroscopically. When comparing the macroscopic appearance of the curettings with the histological appearance, it can be seen that the largest percentage of exact correlation is in the category of POC where 679 of the 1 464 patients (46,4%) showed agreement. While there was considerable overdiagnosis of POC on macroscopic appearance, the main histological finding where POC was not confirmed, was that of decidua. 533 patients (36,4%) had POC diagnosed macroscopically with decidua diagnosed histologically.

Decidua implies the presence of a recent pregnancy, either intrauterine or extrauterine. The features distinguishing true decidua from pseudodecidualisation are shown in Table 3. As only 5 of the patients in the

series had ectopic pregnancies, the remaining 591 patients with the histological diagnosis of decidua may be assumed to have had recent intrauterine pregnancies or abortions. A few of these patients may have had ectopic pregnancies which resolved spontaneously, but this number must be small.

The finding of decidua without villi or trophoblast is known to be a common finding in abortions (Rushton 1987, Nesbitt 1962, Joupilla 1980) and the reasons for this have been discussed previously. In this study the histological findings of POC and decidua have therefore both been used as implying the presence of a recent pregnancy and have been grouped together. Not all tissue submitted for examination is included in the microtomed sections which are examined microscopically. Thus, even if fetal parts or villi were present in some part of the curettings, these would not always be detected on histological examination.

On the basis that POC and decidua both suggest the presence of a recent intrauterine pregnancy, there was a correct correlation between the macroscopic and histological appearances which was compatible with abortion in 1 272 patients (86,9%). The sensitivity of the macroscopic appearance in the diagnosis of abortion was 96,6% with a positive predictive value of 91,6%.

In the study by Lindahl and Ahlgren (1986), the macroscopic and histological appearance of abortion curettings correlated in 46% of cases. This was based on identification of villi in curettings and did not include the finding of decidua only. It does, however, emphasise the importance of careful macroscopic examination of the curettings. In this study the false positive rate was very low. Other studies (Kiel 1986) have shown a much higher rate of identification of

chorionic villi or fetal parts. This is dependent on a number of factors, inter alia the number of sections examined, the completeness of the specimen submitted and processed and the use of special stains in doubtful cases.

In establishing the reliability of using the macroscopic appearance as a screening test in the diagnosis of abortion, the correlation between the macroscopic and histological appearances must be determined. The kappa (k) statistic is a measure of agreement between the two parameters. It is designed to eliminate the agreement which is due to chance alone (Brennan 1992). Other statistical tests such as the chi-squared test and the Student's t test measure association rather than agreement. The kappa statistic is dependent on the prevalence of the attribute being measured. When there is a high underlying prevalence, a high level of agreement is expected. As the kappa relates the observed agreement to the expected agreement, in these circumstances the value might be falsely low.

In this study the kappa value was 0,26, indicating fair agreement between the two tests and this is confirmed by the confidence intervals for kappa which indicate agreement. This, together with the high sensitivity and positive predictive value, shows that macroscopic examination is a good discriminator for the presence of incomplete abortion where the clinical diagnosis is reasonably certain.

It will be seen from Table 6 that where the diagnosis was uncertain with a diagnosis other than incomplete abortion being considered, the results, both in relation to the macroscopic appearance and the histology, were different. Fewer patients had

curettings with the typical appearance of POC. Histological examination confirmed this, as more of the results were reported as endometrium, blood clot, insufficient for analysis or other. In cases where either the clinical diagnosis or the macroscopic appearance of the curettings is atypical, therefore, it is mandatory to send curettings for histological examination.

(b) Exclusion of gestational trophoblastic disease

In order to determine whether gestational trophoblastic disease is likely to be missed if routine histological examination is not carried out, it is necessary to determine the prevalence of this disease, the methods of diagnosis and the number of cases diagnosed for the first time on histology.

While the incidence of gestational trophoblastic disease in South Africa is difficult to determine, in the study period of 11 months, 16 new cases of molar pregnancy were diagnosed. Of these 7 were diagnosed ultrasonographically, most of them having presented with vaginal bleeding after a period of amenorrhoea associated with symptoms of pregnancy. They were therefore investigated as for a threatened abortion. One patient had a partial mole diagnosed on ultrasound examination and the patient underwent Caesarean section. The remaining 8 cases presented clinically as inevitable or incomplete abortions and underwent evacuation of the uterus.

In 7 of the 8 cases the diagnosis was made on macroscopic examination of the curettings and confirmed histologically. In one case the curettings were not regarded as abnormal, but the histological report was of extravillous trophoblast and follow up with HCG

estimations was recommended. This patient defaulted follow-up but presented two months later with persistent bleeding and was treated with chemotherapy and made a complete recovery. The failure of detection of gestational trophoblastic disease by macroscopic examination of curettings is thus 1:1 464.

This figure would probably be lower if the patients excluded from the study were taken into account. These include the 49 patients who were excluded because of incomplete data collection, patients who had therapeutic terminations of pregnancy and patients with missed abortions or blighted ova diagnosed at ultrasound examination. This latter group has a higher incidence of molar change than spontaneous abortions and thus more cases can be expected to be found in these patients (Rushton 1987), where all curettings should be sent for histological examination.

The low incidence of gestational trophoblastic disease diagnosed on routine histological examination of curettings, is borne out by other studies (Tangtrakul 1984, Kiel 1986) where incidences of 1 : 2 533 and 0,015% were reported. In the case reported where gestational trophoblastic disease was missed following a therapeutic termination of pregnancy (DeCherney 1971), the uterus was evacuated by suction curettage. This method of evacuation is commonly employed for terminations of pregnancy rather than curettage of retained products, as in incomplete abortions. As the curettings are distorted by the suction apparatus and often not available for close inspection because they are deposited directly into a sealed receptacle, it is difficult to assess the macroscopic appearance of the tissue removed. This is not the case with evacuations of retained products of spontaneous abortions.

While one case of gestational trophoblastic disease was missed on macroscopic examination in this series, what is possibly more significant is that the other seven cases were all identified. The over diagnosis of trophoblastic disease on macroscopic examination shows a tendency to err on the side of not missing any cases. In the group where the histological diagnosis of extravillous trophoblast was reported, the majority defaulted follow-up. This is unfortunately a common occurrence in the socio-economic climate which is prevalent. Of those who were followed up with HCG estimations, these were all negative or very marginally raised. This report, in most cases, will mean that the placental site has been sampled. As this is difficult to be certain of when only fragmented curettings are available for examination, follow-up is suggested as a precaution.

(c) Exclusion of ectopic pregnancy

The final reason for routine histological examination is to exclude ectopic pregnancy. The significance of endometrial histology in ectopic pregnancy has been debated for many years. While some people would suggest investigating every patient where histology did not show evidence of chorionic villi or trophoblast (Novak 1962, Jeffcoate 1975), this study shows that 46% of incomplete abortions show no evidence of villi or trophoblast and consist of decidua only.

Of the 9 patients with suspected ectopic pregnancies, two were confirmed. The remaining seven patients who did not have ectopic pregnancies had curettings showing either decidua or endometrium. Of the 5 proven ectopic pregnancies, only one showed decidua. Two showed endometrium and the remaining two had insufficient curettings.

This study, like many others (Bobeck 1957, Romney 1950), indicates that the absence of villi on abortion histology does not necessarily imply an ectopic pregnancy. In the majority of cases, in fact, this is not the case. It also shows that there is no type of endometrium which is diagnostic of ectopic pregnancy and that either decidua or endometrium may be obtained. Of the five ectopic pregnancies, 20% had decidua histologically, 40% had endometrium and 40% had insufficient curettings. These results are similar to the study by Ollendorff where 22,6% of patients with ectopic pregnancies had decidua and 58,4% had endometrium. These results are contradicted, however, by Lindahl (1986) who found that 33% of patients who did not have evidence of villi histologically, had ectopic pregnancies. Schafi (1988) also suggests that histology be carried out routinely on specimens from abortions to avoid missing ectopic pregnancies.

The value of routine histological examination of all curettings from abortions needs to be reassessed in the light of the above findings. The time, cost and manpower involved make it important to perform this investigation only when it is necessary. Its contribution to the diagnosis of abortion has been shown to be adequately matched by the macroscopic appearance alone. The role of histology in the diagnosis of ectopic pregnancy is very small and does not warrant the outlay involved.

The incidence of GTD diagnosed for the first time at histology is small and, while it is inevitable that an occasional case may be missed if histological examination is not undertaken, the fact that the disease is curable and is likely to present early with symptoms, must be considered in weighing up the needs for routine histological examination.

8. CONCLUSIONS

This study shows that the precept that histological confirmation of pregnancy by the presence of villi or trophoblast does not apply in practical terms, as many specimens are reported as decidua only.

There is good agreement between macroscopic appearance of curettings and histology in patients with a certain diagnosis of abortion. Where there is uncertainty as to the diagnosis, this correlation is not as good. Thus macroscopic appearance is a good screening test for the diagnosis of abortion and histological examination is only necessary when the clinical diagnosis is in doubt or when the macroscopic appearance of the curettings is atypical.

The finding of trophoblastic disease diagnosed for the first time at histology is low. In this series the diagnosis of gestational trophoblastic disease was made on macroscopic examination in 100% of histologically proven cases. In one case where the histology was equivocal and the patient was subsequently shown to have gestational trophoblastic disease, the diagnosis was not made on macroscopic appearance of the curettings. The incidence in this study was thus 1 : 1 464 or 0,06%.

Histological examination of abortion curettings was not particularly helpful in diagnosing ectopic pregnancy. Many patients with incomplete abortions had decidua only at histology and it would have been unnecessary and time-consuming to investigate all these patients. There was also no type of endometrium specific to ectopic pregnancy. Either decidua or endometrium might be present.

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